Drugs

Follow-up to the January 25, 2008 Early Communication about an Ongoing Data Review for Ezetimibe/Simvastatin (marketed as Vytorin), Ezetimibe (marketed as Zetia), and Simvastatin (marketed as Zocor)

January 8, 2009

This information reflects FDA's current analysis of available data concerning these drugs.

On January 25, 2008, FDA announced that it would be reviewing data from the ENHANCE trial (Effect of Combination Ezetimibe and High-Dose Simvastatin vs. Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia). (Early Communication from 1/25/2008)[1] Preliminary results from this trial had indicated that there was no significant difference between Vytorin and simvastatin-treated patients in the thickness of the carotid (neck) arteries despite greater lowering of LDL (bad) cholesterol with Vytorin compared to simvastatin. The thickness of the carotid arteries, also known as carotid intima-media thickness or cIMT, is a marker of risk for cardiovascular disease. The preliminary results from the ENHANCE trial raised several questions, some of which involve the relationship of cIMT to LDL cholesterol levels and the role of cIMT in drug development.

The FDA has completed its review of the final clinical study report of ENHANCE. Following two years of treatment, carotid artery thickness increased by 0.011 mm in the Vytorin group and by 0.006 mm in the simvastatin group. The difference in the changes in carotid artery thickness between the two groups was **not** statistically significant. However, the levels of LDL cholesterol decreased by 56% in the Vytorin group and decreased by 39% in the simvastatin group. The difference in the reductions in LDL cholesterol between the two groups **was** statistically significant.

The results from ENHANCE do not change FDA's position that an elevated LDL cholesterol is a risk factor for cardiovascular disease and that lowering LDL cholesterol reduces the risk for cardiovascular disease. Based on current available data, patients should not stop taking Vytorin or other cholesterol lowering medications and should talk to their doctor if they have any questions about Vytorin, Zetia, or the ENHANCE trial.

ENHANCE was a randomized, double-blind, active-controlled trial conducted in patients with heterozygous familial hypercholesterolemia (HeFH). A total of 725 patients were randomized 1:1 to receive either Vytorin 10/80 (ezetimibe 10 mg plus simvastatin 80 mg) or simvastatin 80 mg for 2 years. The primary efficacy outcome was the change in ultrasound-determined carotid artery thickness (or cIMT).

Based on data from a previously-conducted cIMT study[1] and the anticipated degree of cholesterol lowering with Vytorin and simvastatin, it was projected that 2 years of treatment with Vytorin in ENHANCE would lead to a *decrease* in cIMT of approximately 0.03 mm whereas treatment with simvastatin would lead to an *increase* in cIMT of approximately 0.02 mm. There are several possible explanations for why the larger reduction in LDL cholesterol observed in the Vytorin group did not translate into significant improvement in cIMT. These include:

- enrollment of a patient population who had received prior lipid-altering or statin therapy and had relatively normal cIMT values at baseline which may make it harder to demonstrate a reduction or improvement in cIMT with Vytorin compared with simvastatin therapy
- the 2-year duration of ENHANCE which may have been too short to see a favorable effect of cholesterol lowering on cIMT
- some other unknown properties of ezetimibe that may negate the beneficial effects of LDL lowering on cIMT.

An ongoing trial known as IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) is examining whether treatment with Vytorin reduces the risk for *cardiovascular events* (composite endpoint of CV death, major coronary events, and stroke) compared with simvastatin alone. This trial of 18,000 patients is scheduled to be completed in 2012. IMPROVE-IT will provide additional data regarding Vytorin's effect on the risk for cardiovascular disease.

Pending the results from IMPROVE-IT, patients should not stop taking Vytorin or other cholesterol lowering medications and should talk to their doctor if they have any questions about these medications.

Ezetimibe (Zetia) is an inhibitor of intestinal cholesterol absorption approved to reduce LDL cholesterol levels. Simvastatin (Zocor) is a lipid-lowering drug ("statin") approved to reduce LDL (bad) cholesterol and increase HDL (good) cholesterol levels and reduce the risk of cardiovascular events such as heart attack and stroke. Vytorin is a combination of ezetimibe and simvastatin approved for reducing LDL and increasing HDL cholesterol levels.

This follow-up communication is in keeping with FDA's commitment to informing the public about its ongoing safety reviews of drugs.

The FDA urges both healthcare professionals and patients to report side effects from the use of lipid lowering drugs to the FDA's MedWatch Adverse Event Reporting program, using the contact information at the bottom of this page.

[1] Smilde T, et al. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolemia (ASAP): a prospective, randomized double-blind study; *Lancet* 2001;357:577-581.

Related information

- Ezetimibe/Simvastatin (marketed as Vytorin) Information[2]
- Early Communication about an Ongoing Data Review for Ezetimibe/Simvastatin (marketed as Vytorin), Ezetimibe (marketed as Zetia), and Simvastatin (marketed as Zocor)[3]
- Early Communication About an Ongoing Safety Review of Ezetimibe/Simvastatin (marketed as Vytorin), Simvastatin (marketed as Zocor) and Ezetimibe (marketed as Zetia) - FDA Investigates a Report from the SEAS Trial (8/21/08)[4]

Contact Us

- **Report a Serious Problem**
- 1-800-332-1088
- 1-800-FDA-0178 Fax

  MedWatch Online[5]

  Regular Mail: Use postage-paid FDA Form 3500[6]

  Mail to: MedWatch 5600 Fishers Lane

Rockville, MD 20857

Links on this page:

1. /Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm070779.htm
2. /Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103324.htm
3. /Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm070779.htm
4. /Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm162899.htm
5. https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm
6. http://www.fda.gov/downloads/Safety/MedWatch/DownloadForms/UCM082725.pdf